Questions & Answers about . . .

Heritable Disorders of Connective Tissue

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
National Institutes of Health
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You can also find this booklet on the NIAMS Web site at www.niams.nih.gov/hi/topics/connective/connective.htm.

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Information Box

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This fact sheet describes a family of more than 200 disorders that affect connective tissues. These disorders result from alterations (mutations) in genes responsible for building tissues. Alterations in these genes may change the structure and development of skin, bones, joints, heart, blood vessels, lungs, eyes, and ears. Some mutations also change how these tissues work.

All of these diseases are directly related to mutations in genes, and thus are called "heritable." Some other connective tissue problems are not directly linked to mutations in tissue-building genes, although some people may be genetically predisposed to becoming affected. The disorders discussed in this fact sheet are called heritable (genetic) disorders of connective tissue (HDCTs). Many, but not all, of them are rare. (See the box on pages 2 and 3 for a description of some of the more common HDCTs.)

What Is Connective Tissue?

Connective tissue is the material between the cells of the body that gives tissues form and strength. This "cellular glue" is also involved in delivering nutrients to the tissue, and in the special functioning of certain tissues. Connective tissue is made up of dozens of proteins, including collagens, proteoglycans, and glycoproteins. The combination of these proteins can vary between tissues. The genes that encode these proteins can harbor defects or mutations, which can affect the functioning of certain properties of connective tissue in selected tissues. This can lead to a HDCT.

Some Common Heritable Connective Tissue Disorders

Physicians and scientists have identified more than 200 heritable connective tissue disorders. Some of the more common ones are listed below. Some of these are really groups of disorders and may be known by other names.

Ehlers-Danlos syndrome—The problems present in Ehlers-Danlos syndrome (EDS), a group of approximately 10 disorders, include changes in the physical properties of skin, joints, blood vessels, and other tissues such as ligaments and tendons. People with EDS have some degree of joint looseness, fragile small blood vessels, and abnormal scar formation and wound healing. Soft, velvety skin stretches excessively but returns to normal after being pulled. Some forms of EDS can present problems with the spine, including curved spine; the eyes; and weak internal organs, including the uterus, intestines, and large blood vessels. Mutations in several different genes are responsible for different symptoms in the several types of EDS. In most cases, the genetic defect involves collagen, the major protein-building material of bone.

Epidermolysis bullosa—The characteristic feature of epidermolysis bullosa (EB) is blistering in the skin. Some forms of the disease may involve the gastrointestinal tract, the pulmonary system, muscle, or the bladder. Most forms are evident at birth. This disorder can be

both disabling and disfiguring, and some forms may lead to early death. The disease results when skin layers separate after minor trauma. Defects of several proteins within the skin are at fault.

Marfan syndrome—People with Marfan syndrome tend to have excessively long bones and are commonly thin, with long, "spider-like" fingers. Other problems include skeletal malformations, abnormal position of the lens of the eye, and enlargement at the beginning part of the aorta, the major vessel carrying blood away from the heart. If left untreated, an enlarged aorta can lead to hemorrhage and even death. This disorder results from mutations in the gene that makes fibrillin-1, a protein important to connective tissue.

Osteogenesis imperfecta—People with osteogenesis imperfecta (OI) have bones that fracture easily, low muscle mass, and joint and ligament laxity. There are four major types of OI ranging in severity from mild to lethal. The appearance of people with OI varies considerably. Individuals may also have a blue or gray tint to the sclera (whites of the eyes), thin skin, growth deficiencies, and fragile teeth. They may develop scoliosis, respiratory problems, and hearing loss. Also known as "brittle bone disease," this disorder arises from mutations in the two genes that make type I collagen, a protein important to bones and skin. These mutations cause the body to make either too little or poor-quality type I collagen.

How Do People Get Gene Alterations?

Either people inherit an altered gene from either or both parents, or—more rarely—an alteration occurs in a copy of the gene during the formation of the egg or sperm that gives rise to the individual. We have two copies of most genes: ones that we inherited from each parent. Males have one copy of each gene on the X chromosome, because they have only one X chromosome, and one copy of each gene on the Y chromosome. In contrast, women have two X chromosomes and therefore have two copies of X chromosome genes.

Some genetic disorders require that only a single copy of a gene be altered. These disorders can be inherited in many generations of a family because the altered copy of the gene can be passed from parent to child (dominant inheritance). The same disorder can occur in an individual without a family history of the condition if there is a new mutation in the right gene in either the egg or sperm that gives rise to that person. Some disorders are seen only when the individual has received an altered copy of the gene from each parent (recessive inheritance); in these families, the person with only a single copy is called a "carrier" and is not actually affected.

If a mutation occurs on an X chromosome, it generally produces a condition in which the pattern of affected individuals in a family is unusual. Often, women are carriers (that is, they have only a single altered copy of the gene), but

males show the condition because they do not have a second protective copy of the gene. Such a condition is referred to as "X-linked."

Who Gets HDCTs?

Scientists estimate that as many as 1 million people in the United States may have a heritable disorder of connective tissue. Generally, these conditions affect people of all ethnic groups and ages, and both genders are commonly affected. Many of these disorders are rare. Some may not be evident at birth, but only declare themselves after a certain age or after exposure to a particular environmental stress.

Does Anything Increase the Chances of Having a Genetic Disease?

Several factors increase the likelihood that a person will inherit an alteration in a gene. If you are concerned about your risk, you should talk to your health care provider or a genetic counselor.

The following factors may increase the chance of getting or passing on a genetic disease:

- Parents who have a genetic disease
- A family history of a genetic disease

- Parents who are closely related or part of a distinct ethnic or geographic community

- Parents who do not show disease symptoms, but "carry" a disease gene in their genetic makeup (this can be discovered through genetic testing).

How Does Genetic Counseling Help?

People seek genetic counseling to help them make better decisions about their lives and families. Because genetic counselors understand how genetic disorders are passed on through families, they can help couples estimate the risks of having children with genetic diseases. They can also tell parents about tests to determine if people are carrying certain altered genes, tests for newborns who may have inherited certain altered genes, and tests that can be done in early pregnancy to determine if a fetus either carries an altered copy of a gene or is affected with a disorder. The information derived from all these studies can be valuable aids in family planning.

Your health care team can help you find genetic counseling if you wish to better understand your disease or risk of disease.

What Are the Symptoms of a HDCT?

Each disorder has different symptoms. For instance, some diseases, such as Marfan syndrome, osteogenesis imperfecta, and certain chondrodysplasias (disorders of long-bone development) cause bone growth problems. People with bone growth disorders may have brittle bones or bones that are too long or too short. In some of these disorders, joint looseness or joints that are too tight can cause problems.

The skin can be affected as well. Ehlers-Danlos syndrome results in stretchy or loose skin, while in the disease cutis laxa, deficient elastic fibers cause the skin to hang in folds. Epidermolysis bullosa results in blistered skin. Pseudoxanthoma elasticum causes skin, eye, and heart problems, and closed-off or blocked blood vessels. Marfan syndrome and some forms of Ehlers-Danlos syndrome lead to weak blood vessels. Some disorders cause people to be unusually tall (Marfan syndrome) or short (chondrodysplasias, osteogenesis imperfecta), or to have head and facial structure malformations (Apert syndrome, Pfeiffer syndrome).

It is critical for affected individuals and their family members to work closely with their health care teams. Symptoms of HDCTs are extremely variable, and some disorders can pose severe health risks even when affected individuals have no symptoms.

How Do Doctors Diagnose HDCTs?

Diagnosis always rests first on a combination of family history, medical history, and physical examination. Because many of these conditions are uncommon, the family physician may suspect a diagnosis but be uncertain about how to confirm it. At this point, referral to experienced clinicians, often medical geneticists, can be extremely valuable either to confirm or to exclude the suspected diagnosis. Laboratory tests are available to confirm the diagnosis for many HDCTs, but not for all.

Once a diagnosis is made, laboratory studies may be available to provide some or all of the following:

- Prenatal testing to identify an affected fetus to assist in family planning.
- Newborn screening to spot a condition that may become evident later in life.
- Carrier testing to identify adults who, without symptoms, carry a genetic mutation for a disease.
- Predictive testing to spot people at risk for developing a genetic connective tissue disease later in life. These tests are helpful for diseases that run in the family.

What Treatments Are Available?

Each disorder requires a specific program for management and treatment. In most instances, regular monitoring is important to assess, for example, diameter of the aorta in people with Marfan syndrome, extent of scoliosis (spine curvature) in people with OI or some forms of EDS, and whether there is protrusion of the spine into the base of the skull in people with OI. For some conditions, specific metabolic treatment is useful (for example, vitamin B_6 in people with homocystinuria, a metabolic disorder resulting from a liver enzyme deficiency). In others, systemic treatment with drugs like beta blockers is appropriate. Maintaining general health is also important for people with all HDCTs, as is staying in touch with specialists who will be aware of emerging new treatments.

What Research Is Being Done on HDCTs?

Scientists are working to better understand these disorders at several levels: (1) to identify the genes in which the mutations reside, (2) to identify the mutations that result in the condition, (3) to understand how these mutations result in the clinical condition, and (4) to use all available information about the condition to plan new therapies and to test their use and value, both in animal models and in affected individuals. Because most of these conditions are uncommon, and individuals with them are widely scattered, it is

often difficult to gather information about the clinical course of the disorder and to assemble enough people to plan effective clinical trials. In addition, genetic changes can sometimes be influenced by lifestyle and environment.

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), a part of the National Institutes of Health (NIH), is the lead Federal agency for connective tissue research. Several other NIH institutes are also studying HDCTs. The NIAMS supports research through grants to scientists around the country, in national and international clinical trials, and at the NIH campus itself. Here is some of the research that is being done:

- The NIAMS is conducting an in-depth natural history study of people who have Marfan syndrome (which leads to abnormally long bones), nail-patella syndrome (a congenital skeletal disorder), Stickler syndrome (which causes eye and joint problems), and Ehlers-Danlos syndrome (which causes skin and blood vessel problems). All of these disorders have multiple, interrelated symptoms. NIAMS scientists are studying these people closely and over a long period to get a more complete picture of the diseases. They hope to improve their understanding of the genetic origins of the symptoms, of disease progression, and of mutations in patients and their relatives. Scientists expect their findings to apply to other HDCTs as well.

- The NIAMS is supporting a study looking for ways to treat diseases such as osteogenesis imperfecta by using gene therapy. Stem cells, which have the potential to develop into more specialized cells, would replace bone cells that have gene defects. This research is being conducted on specially bred mice.

- Another NIAMS project is examining gene defects that lead to abnormal elastin, the connective tissue protein that allows arteries, muscles, and other organs to respond in certain ways to movement. So far, the investigators have shown how elastin gene mutations cause two specific diseases: a skin disease (cutis laxa) and a blood vessel disease (supravalvular aortic stenosis). Scientists hope to learn more about how mutations affect elastin fiber and tissue growth. They also hope to find out how gene defects lead to the development of elastin disease.

- The NIAMS is encouraging the establishment of new research registries for connective tissue disorders and other conditions. These registries would support the collection of demographic and medical data from patients and families to be used in research on disorders. Epidermolysis bullosa is one of the disorders for which the Institute has already established a research registry.

Other NIAMS researchers are exploring

- the chemistry and biology of elastin genes
- collagen gene defects (several types) that cause bone diseases
- collagen IV gene defects in mice and in humans (Alport syndrome)
- proteoglycans, a group of proteins that maintain tissue stiffness
- fibroblasts, cells that form the fibrous tissues in the body
- cartilage, joints, and skin layers.

Ongoing studies of aneurysms—a weak spot in a blood vessel wall that threatens to burst—are taking place at several NIH Institutes. Aneurysms can prove deadly to people with Marfan syndrome and other HDCTs. These studies have been helped by a pioneering project at the NIAMS that developed a breed of mice prone to aneurysms. Scientists hope the mutant mice will improve understanding of aneurysms and ways to prevent them.

At the National Institute of Child Health and Human Development, scientists are working with young patients who have osteogenesis imperfecta. They hope to learn more about the genetics of the disease and the natural history of the many secondary features involved, as well as rehabilitation techniques. Research is also ongoing in animal models and human clinical trials into the use of bisphosphonates—drugs used to treat osteoporosis.

The National Human Genome Research Institute is conducting a clinical study of mind-body therapy for chronic pain in people with Ehlers-Danlos syndrome. At the National Eye Institute, research is being supported on alterations in the gene that causes pseudoxanthoma elasticum (PXE) and on which variations cause different signs and symptoms. And scientists at the National Institute of Dental and Craniofacial Research are carrying out clinical studies on fibrous dysplasia of bone.

Where Can People Find More Information About HDCTs?

People with HDCTs can contact professional and support groups that can supply more detailed information than is found here. Most of them also have Internet Web sites. Some major groups are listed below.

- **National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)**
  National Institutes of Health
  1 AMS Circle
  Bethesda, MD 20892–3675
  Phone: 301–495–4484 or
  877–22–NIAMS (226–4267) (free of charge)
  TTY: 301–565–2966
  Fax: 301–718–6366
  E-mail: NIAMSInfo@mail.nih.gov
  www.niams.nih.gov

- **American Academy of Dermatology**
  P.O. Box 4014
  Schaumburg, IL 60168–4014
  Phone: 847–330–0230 or
  888–462–DERM (3376) (free of charge)
  Fax: 847–330–0050
  www.aad.org

- **American Academy of Orthopaedic Surgeons**
  P.O. Box 2058
  Des Plaines, IL 60017
  Phone: 800–824–BONE (2663) (free of charge)
  www.aaos.org

- **Coalition for Heritable Disorders of Connective Tissue**
  Coalition for Heritable Disorders of Connective Tissue
  4301 Connecticut Ave, N.W., Suite 404
  Washington, DC 20008
  Phone: 202–362–9599
  E-mail: chdct@pxe.org
  www.chdct.org

- **Genetic Alliance**
  4301 Connecticut Avenue, N.W., Suite 404
  Washington, DC 20008
  Phone: 202–966–5557 or
  800–336–GENE (4363) (free of charge)
  Fax: 202–966–8553
  www.geneticalliance.org

- **National Organization for Rare Disorders, Inc.**
  P.O. Box 8923
  New Fairfield, CT 06812–8923
  Phone: 203–746–6518 or 800–999–6673 (free of charge)
  Fax: 203–746–6481
  www.rarediseases.org

- **National Society of Genetic Counselors, Inc.**
  233 Canterbury Drive
  Wallingford, PA 19086–6617
  Phone: 610–872–7608
  E-mail: nsgc@aol.com
  www.nsgc.org

- **Dystrophic Epidermolysis Bullosa Research Association (D.E.B.R.A.) of America**
  5 West 36th Street, Suite 404
  New York, NY 10018
  Phone: 212–868–1573
  Fax: 212–868–9296
  E-mail: staff@debra.org
  www.debra.org

- **Ehlers-Danlos National Foundation (EDNF)**
  6399 Wilshire Boulevard, Suite 200
  Los Angeles, CA 90048
  Phone: 323–651–3038
  Fax: 323–651–1366
  E-mail: staff@ednf.org
  www.ednf.org

- **National Association for Pseudoxanthoma Elasticum, Inc.**
  8764 Manchester Road, Suite 200
  St. Louis, MO 63144
  Phone: 314–962–0100
  Fax: 314–962–0100
  E-mail: pxenape@estreet.com
  www.napxe.org

- **National Marfan Foundation**
  22 Manhasset Avenue
  Port Washington, NY 11050–2023
  Phone: 516–883–8712
  800–8–MARFAN (862–7326) (free of charge)
  Fax: 516–883–8040
  E-mail: staff@marfan.org
  www.marfan.org

- **Osteogenesis Imperfecta Foundation**
  804 West Diamond Avenue, Suite 210
  Gaithersburg, MD 20878
  Phone: 800–981–2663 (free of charge)
  Fax: 301–947–0456
  E-mail: bonelink@oif.org
  www.oif.org

- **PXE International**
  4301 Connecticut Avenue NW, Suite 404
  Washington, DC 20008
  Phone: 202–362–9599
  Fax: 202–966–8553
  E-mail: pxe@pxe.org
  www.pxe.org

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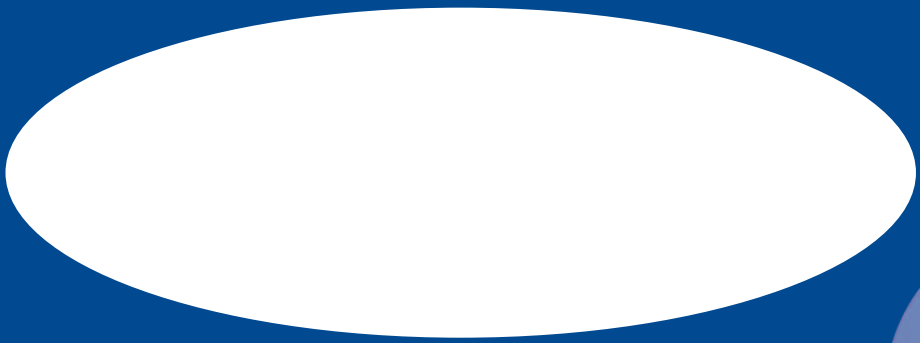
The mission of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), a part of the Department of Health and Human Services' National Institutes of Health (NIH), is to support research into the causes, treatment, and prevention of arthritis and musculoskeletal and skin diseases, the training of basic and clinical scientists to carry out this research, and the dissemination of information on research progress in these diseases. The National Institute of Arthritis and Musculoskeletal and Skin Diseases Information Clearinghouse is a public service sponsored by the NIAMS that provides health information and information sources. Additional information can be found on the NIAMS Web site at www.niams.nih.gov.



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